Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1.   (Currently amended) A computer implemented method for modeling ligand-protein
binding interactions, comprising the steps of:

   providing to a computer processor structural information describing the structure
      of a protein and each ligand in a set of one or more ligands;

   using the structural information for the protein to identify a binding region of the
      protein;

   identifying a plurality of preferred binding conformations for each ligand in the
      set of ligands in the binding region, the preferred binding conformations
      being determined by generating a set of configurations for each ligand by
      applying a coarse-grained docking algorithm and ranking initial
      conformations for each ligand in the set of ligands at the binding region
      using energy scoring;

   optimizing the preferred binding conformations using annealing molecular
      dynamics, the annealing molecular dynamics including solvation effects;

   calculating a binding energy for each ligand in the set of ligands in the
      corresponding optimized preferred binding conformations; and

   selecting for each ligand in the set of ligands the lowest calculated binding energy
      in the optimized preferred binding conformations, and outputting the
      selected calculated binding energies as the predicted binding energies for
      the predicted binding conformations of the set of ligands,

<u>wherein the method steps are performed by a programmable processor executing a</u>

<u>program of instructions</u>.

2.   (Currently amended) The method of claim 1, wherein[[:]] the binding region is a known

binding region defined by the structural information.

3.   (Previously presented) The method of claim 1, wherein:

the binding region is an unknown binding region; and

using the structural information for the protein to identify a binding region of the

protein comprises predicting a probable binding region based at least in

part on the structural information.

4.   (Currently amended) The method of claim 3, wherein using the structural information to

identify a binding region of the protein comprises:

mapping the empty volumes available for ligand binding in the protein to identify

one or more potential binding regions;

generating initial conformations for one or more ligands known to bind the

protein using a coarse-grained docking algorithm in each of the one or

more potential binding regions and scoring a̲n energy function for the

initial conformations;

selecting from the initial conformations for each of the known ligands a plurality

of best conformations in each of the potential binding regions based at

least in part on the preliminary energy scores; and

identifying the probable binding site based on a spatial location of the best

conformations.

5.   (Currently amended) The method of claim 4, further comprising[[:]] optimizing the

selected best conformations to obtain a set of energy-minimized conformations for each

of the known ligands in each of the potential binding regions and scoring an energy

function for each of the best conformations[[;]], wherein identifying the probable binding

site is based on a spatial location of the best conformations having the lowest energy

scores.

6.   (Currently amended) The method of claim 4, further comprising[[:]] before scoring the

energy function for each of the best conformations, calculating for each of the best

conformations a percentage of the ligand surface area buried within the protein for the

conformation[[;]], wherein the energy function is scored only for a subset of the best

conformations, wherein each of the best conformations in the subset has a calculated

percentage of the ligand surface area buried within the protein which exceeds a

predetermined threshold.

7.   (Cancelled)

8.   (Currently amended) The method of claim 1, wherein[[:]] identifying a plurality of

preferred binding conformations includes optimizing the selected best conformations to

obtain a set of energy-minimized conformations for each of the ligands[[;]], wherein the

preferred binding conformations comprise the energy-minimized conformations.

9.   (Currently amended) The method of claim 1, wherein[[:]] the annealing molecular

dynamics includes a full atom force field.

10.   (Currently amended) The method of claim 1, wherein[[:]] the solvation effects include a

continuum description of solvation.

11.   (Currently amended) The method of claim 1, wherein[[:]] the solvation effects include a

surface-area based solvation model.

12. (Currently amended) The method of claim 1, wherein[[:]] calculating a binding energy for each ligand in the set of ligands includes taking the difference in the ligand energy in the protein and in solution.

13. (Currently amended) The method of claim 1, wherein[[:]] the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the ligand in water from the energy of the ligand in the protein.

14. (Currently amended) The method of claim 1, wherein[[:]] the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein.

15. (Currently amended) The method of claim 1, further comprising[[:]] identifying from the set of ligands one or more ligands predicted to have high binding affinity based on the calculated binding energy of the ligands in the binding site.

16. (Currently amended) The method of claim 1, wherein[[:]] the protein is a globular protein or a transmembrane protein.

17.-28. (Cancelled)

29. (Currently amended) A computational model of a ligand-protein complex for a protein having an unknown binding site, the model comprising[[:]] a computer-readable memory storing data describing an optimized preferred binding conformation for the protein and a ligand known to bind to the protein, the optimized binding conformation being generated according to the method of claim 1.

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30.   (Cancelled)

31.   (Currently amended) A computer program product on a computer-readable medium for modeling ligand-protein binding interactions, the computer program product comprising instructions operable to cause a programmable processor to:

> provide structural information describing the structure of a protein and each ligand in a set of one or more ligands;

> use the structural information for the protein to identify a binding region of the protein;

> identifying a plurality of preferred binding conformations for each ligand in the set of ligands in the binding region, the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a coarse-grained docking algorithm and ranking initial conformations for each ligand in the set of ligands at the binding region using energy scoring;

> optimize the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects;

> calculate a binding energy for each ligand in the set of ligands in the corresponding optimized preferred binding conformations; and

> select for each ligand in the set of ligands the lowest calculated binding energy in the optimized preferred binding conformations, and output the selected calculated binding energies as the predicted binding energies for the predicted binding conformations for each of the set of ligands.

32.-35. (Cancelled)

36.   (Currently amended) The computer program product of claim 31, wherein the instructions to use the structural information to identify a binding region of the protein comprise[[s]] instructions to:

    map the empty volumes available for ligand binding in the protein to identify one or more potential binding regions;

    generate initial conformations for one or more ligands known to bind the protein using docking techniques in each of the one or more potential binding regions and scoring an energy function for the ~~intial~~ initial conformations;

    select from the initial conformations for each of the known ligands a plurality of best conformations in each of the potential binding regions based at least in part on the preliminary energy scores; and

    identify the probable binding site based on a spatial location of the best conformations.

37.   (Currently amended) The computer program product of claim 31, wherein[[:]] the annealing molecular dynamics includes a full atom force field.

38.   (Currently amended) The computer program product of claim 31, wherein[[:]] the solvation effects include a continuum description of solvation.

39.   (Currently amended) The computer program product of claim 31, wherein[[:]] the solvation effects include a surface-area based solvation model.

40.   (Currently amended) The computer program product of claim 31, wherein the instructions to calculate a binding energy for ligand in the set of ligands include[[s]] taking the difference in the ligand energy in the protein and in solution.

41.   (Currently amended) The computer program product of claim 31, wherein[[:]] the binding energy is calculated for a ligand according to a scoring function comprising substracting subtracting the free energy of the ligand in water from the energy of the ligand in the protein.

42.   (Currently amended) The computer program product of claim 31, wherein[[:]] the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein.

43.   (Currently amended) The computer program product of claim 31, further comprising instructions to[[:]] identify from the set of ligands one or more ligands predicted to have high binding affinity based on the calculated binding energy of the ligands in the binding site.

44.   (Currently amended) The computer program product of claim 31, wherein[[:]] generating and ranking initial conformations includes scoring an energy function for at least some of the initial conformations and ranking the initial conformations based at least in part on the energy scores.

45.   (Currently amended) The computer program product of claim 31, wherein[[:]] generating and ranking initial conformations includes determining a percentage of the ligand surface area buried within the protein for each of the initial conformations and determining energy scores only for a subset of the preferred conformations, wherein each of the preferred conformations in the subset has a calculated percentage of the ligand surface area buried within the protein which exceeds a predetermined threshold.

46.   (New) A computer implemented method for modeling ligand-protein binding interactions, comprising the steps of:

provided structural information describing the structure of a protein and each ligand in a set of one or more ligands;

using the structural information for the protein to identify a binding region of the protein;

identifying a plurality of preferred binding conformations for each ligand in the set of ligands in the binding region, the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a coarse-grained docking algorithm and ranking initial conformations for each ligand in the set of ligands at the binding region using energy scoring;

optimizing the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects;

calculating a binding energy for each ligand in the set of ligands in the corresponding optimized preferred binding conformations, the binding energy being calculated according to a scoring function selected from the group consisting of subtracting the free energy of the ligand in water from the energy of the ligand in the protein and subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein; and

selecting for each ligand in the set of ligands the lowest calculated binding energy in the optimized preferred binding conformations, and outputting the selected calculated binding energies as the predicted binding energies for the predicted binding conformations of the set of ligands,

wherein the method steps are performed by a programmable processor executing a program of instructions.

47.   (New) A computer program product on a computer-readable medium for modeling
       ligand-protein binding interactions, the computer program product comprising
       instructions operable to cause a programmable processor to:

              provide structural information describing the structure of a protein and each
                     ligand in a set of one or more ligands;

              use the structural information for the protein to identify a binding region of the
                     protein;

              identify a plurality of preferred binding conformations for each ligand in the set of
                     ligands in the binding region, the preferred binding conformations being
                     determined by generating a set of configurations for each ligand by
                     applying a coarse-grained docking algorithm and ranking initial
                     conformations for each ligand in the set of ligands at the binding region
                     using energy scoring;

              optimize the preferred binding conformations using annealing molecular
                     dynamics, the annealing molecular dynamics including solvation effects;

              calculate a binding energy for each ligand in the set of ligands in the
                     corresponding optimized preferred binding conformations, the binding
                     energy being calculated according to a scoring function selected from the
                     group consisting of subtracting the free energy of the ligand in water from
                     the energy of the ligand in the protein and subtracting the free energy of
                     the protein and the free energy of the ligand from the free energy of the
                     ligand in the protein; and

              select for each ligand in the set of ligands the lowest calculated binding energy in
                     the optimized preferred binding conformations, and output the selected
                     calculated binding energies as the predicted binding energies for the
                     predicted binding conformations for each of the set of ligands.